

- WO 2004/058779 A method of phosphorodiamidite production which method 1. comprises the steps of reacting a phosphorus trihalide with a dialkyl amine in a polar solvent to form an intermediate compound and subsequently reacting the intermediate copound with a hydroxyalkyl compound and a dialkyl amine, in the presence of a non-polar co-solvent.
 - A method as claimed in Claim 1 in which the phosphorus trihalide 2. 10 is phosphorus trichloride.
 - A method as claimed in Claim 1 in which the phosphorus trihalide 3. is phosphorus tribromide.
 - A method according to any one of Claims 1 to 3 in which the 15 4. dialkyl amine is diisopropylamine.
 - A method as claimed in any one of Claims 1 to 3 in which the 5. dialkyl amine is selected from the group consisting of dimethylamine, diethylamine, di-n-propylamine, di-n-butylamine, di-isobutylamine or di-20 tert-butylamine.
 - A method as claimed in any one of the preceding claims in which 6. the polar solvent is a nitrile compound.
 - 7. A method as claimed in Claim 6 in which the nitrile compound is acetonitrile.
 - 8. A method as claimed in Claim 6 in which the polar solvent is 30 propionitrile or benzonitrile.

25

- 9. A method as claimed in any one of the preceding claims in which the hydroxyalkyl compound is hydroxypropionitrile.
- 10. A method as claimed in any one of Claims 1 to 8 in which the hydroxyalkyl compound is methanol or tert-butyl alcohol.
 - 11. A method as claimed in any one of Claims 1 to 10 in which the alkane co-solvent is a C_5 to C_9 aliphatic hydrocarbon.
- 10 12. A method as claimed in any one of Claims 1 to 10 in which the alkane co-solvent is an alicyclic hydrocarbon.
 - 13. A method according to any one of the preceding claims in which the ratio of polar solvent to non-polar solvent is 1:1.
 - 14. A phosphorodiamidite compound produced by the method of any one of Claims 1 to 13 and having the General Formula (I):

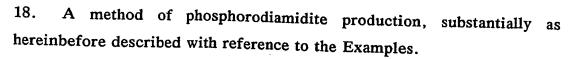
$(R_2 N)_2$ -P-O(CH₂)_n-CN (I)

20

15

wherein R is a C_1 to C_4 alkyl, hydroxyalkyl or oxyalkyl group; and n is a whole number of from 1 to 4.

- 15. A compound according to Claim 14 which is 2-cyanoethyl 25 tetraisopropyl phosphorodiamidite.
 - 16. The use of a compound as claimed in Claim 14 or Claim 15 as made by the method of claim 1 in the synthesis of oligonucleotides.
- 30 17. A phosphorodiamidite compound, substantially as hereinbefore described with reference to the Examples.



19. The use of a phosphorodiamidite compound, substantially as hereinbefore described with reference to the Examples.